

**Dysfunctional brain circuits in psychiatry: new targets for deep brain stimulation?**

**A.F. Ten Brink (3268675)**

**Neuroscience and Cognition**

**October 2, 2013**

|  |  |
| --- | --- |
| **First Examiner**  Dr. Geert M.J. Ramakers  Department of Neuroscience and Pharmacology  Utrecht University | **Daily Supervisor**  Dr. Martijn Figee  Department of Psychiatry  Academic Medical Centre, University of Amsterdam |
| **Second Examiner**  Prof. dr. Damiaan Denys  Department of Psychiatry  Academic Medical Centre, University of Amsterdam | **Track Coordinator**  Prof. dr. Albert Postma  Department of Experimental Psychology  Utrecht University |
|  |  |

**Abstract**

Understanding mechanism of action of deep brain stimulation (DBS) on a neural level contributes to new insights concerning brain circuits underlying neuropsychiatric disorders, which seem to overlap. Studying the neural effects of DBS on emotion, cognition and behavior allows for a shift from the current diagnostic classification of psychiatric disorders towards dysfunctional circuits. Effects of DBS throughout the brain for different targets for obsessive-compulsive disorder, major depressive disorder, Tourette syndrome and Anorexia Nervosa are described by reviewing structural and functional imaging studies.

**List of abbreviations**

ACC anterior cingulate cortex

ALIC anterior limb of the internal capsule

AN Anorexia Nervosa

BOLD blood oxygen level dependent

CSTC cortical-striatal-thalamic-cortical

CT computed tomography

DBS deep brain stimulation

DTI diffusion tensor imaging

EEG electroencephalogram

fMRI functional magnetic resonance imaging

GPi globus pallidus internus

ITP inferior thalamic penduncle

LHb lateral habenula

NAc nucleus accumbens

MFB medial forebrain bundle

MPTP 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

OCD obsessive-compulsive disorder

OFC orbitofrontal cortex

PD Parkinson’s disease

PET positron emission tomography

PFC prefrontal cortex

SCG subgenual cingulated gyrus

SPECT single-photon emission computed tomography

SSRI selective serotonin reuptake inhibitors

STN subthalamic nucleus

TS Tourette syndrome

VC ventral [anterior internal] capsule

VS ventral striatum

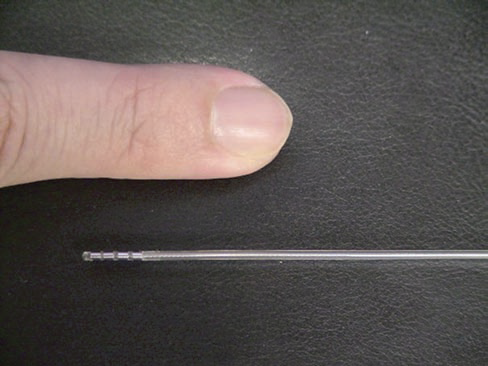
**Introduction**

Diagnostic classification in psychiatry is a highly debated topic. The Diagnostic and Statistical Manual (DSM-IV-TR) is despite many pitfalls, currently the best available diagnostic tool and therefore widely used. However, diagnosis of mental disorders in the DSM-IV is based on clinical observation and patients’ phenomenological symptom reports, without any link to underlying brain circuits. Since the development of neuroimaging, psychiatrists try to discover typical neural activation patterns that can be matched with certain disorders. Imaging the brain at rest, during performance of cognitive tasks or during symptom provocation can reveal dysfunctional brain circuits. Knowledge about these brain circuits can be of great importance in understanding the origins of psychiatric disorders and may help developing new treatment strategies. Currently it has become apparent that several treatments, including drug therapies and psychotherapies, may be effective by modulating the function of these circuits. Moreover, new treatment techniques for patients who are refractory to medication or psychotherapy seem to be more directly designed to modulate brain circuits. These include transcranical stimulation (TMS), vagus nerve stimulation, transcranial direct current stimulation (tDCS) and deep brain stimulation (DBS). These techniques are only used in severely ill, treatment refractory patients. Nevertheless, global response rates range from 40 to 60%. DBS may be the most promising new candidate because unlike other techniques, DBS can induce chronic but reversible changes in subcortical brain circuits that are relevant for most mental disorders. Moreover, studying the mechanism of action of DBS on a neural level may contribute to new insights concerning brain circuits underlying neuropsychiatric disorders. Studying the neural effects of DBS on emotion, cognition and behavior may allow for a shift from the current diagnostic classification of psychiatric disorders towards dysfunctional circuits. In this review, background information including the procedure and history of DBS is described in order to understand how theory’s about mechanisms of DBS evolved. The effects of DBS throughout the whole brain are identified by looking at DBS neuroimaging studies in several psychiatric disorders, including obsessive-compulsive disorder (OCD), major depressive disorder (MDD), Tourette syndrome (TS) and Anorexia Nervosa (AN).

*Procedure of DBS*

|  |
| --- |
| **Figure 1.** Permanent deep brain stimulation electrode. Note four contacts at distal end of lead, each 1.5 mm in length. Derived from Lyons, 2011. |

DBS is a surgical treatment that involves the implantation of a medical device that sends electrical impulses to specific brain areas. The device is composed of two wires, the lead and extension, and a programmable pulse generator. The pulse generator sends electrical impulses to the tip of the lead wire, where at least four electrodes are located (see Figure 1). These electrodes can vary in material, size and shape, which affect the properties of the electrical stimulation. The surgical procedure is usually performed with the patient awake. In this way, the target can be stimulated by microelectrode recordings to aid placement of the permanent electrode. Furthermore, computed tomography (CT) or functional magnetic resonance imaging (fMRI) scans are used to localize the desired target. The scalp is locally anesthetized and a burr hole is made into the skull. Then, the electrode is placed on the specific target and connected to the pulse generator that is implanted in a second session (see Figure 2). Lead extensions and



|  |
| --- |
| **Figure 2.** Postoperative X-ray demonstrating the implantable pulse generator (a), extension cables and DBS electrodes (b). Derived from Blomstedt, 2011. |

the pulse generator are implanted subcutaneously (Farris & Giroux, 2011; Lozano & Lipsman, 2013; Lyons, 2011). The pulse generator can be programmed externally with many different possible settings. First of all, the polarity of the stimulation can vary, whereby in humans monopolar stimulation is preferred over bipolar stimulation. Other therapeutic stimulation parameters vary generally for voltage of current from 1 to 6 V, for pulse duration from 60 to 200 μs and for stimulation frequency from 120 to 180 Hz (Kuhn et al., 2010; Volkmann et al., 2006). Stimulation is usually continuously given, but rapidly cycled on- and off-stimulation is also possible. At any time, online adjustments can be made in order to reduce side effects and maximize desired treatment effects. Programming may take a couple of months, until maximal improvement is reached.

*Advantages and side effects*

There are many advantages of DBS over other methods. First of all, compared to ablative neurosurgery, no irreversible lesioning is needed and if necessary, electrodes can be removed. Furthermore, the stimulation variables can be adjusted any time, for each patient individually. Therefore, in case of side effects the stimulation can be immediately stopped or changed. Since DBS can be turned on and off every moment, randomized double-blind controlled clinical trials are easily conducted. In this way, the actual stimulation effects can be differentiated from placebo effects or effects due to microlesioning from electrode insertion (Lozano & Lipsman, 2013). Additionally, changes in brain activity that are due to DBS can be measured by using recordings that can be made through the implanted electrodes, or by neuroimaging (Limousin et al., 1997). Finally, an important advantage of DBS is that it lacks most of the long-term side effects that are associated with medications used in psychiatry such as antidepressants (Schlaepfer et al., 2011).

Treatment with DBS is not without risk and much research is done to assess safety. DBS related complications can be classified as (1) perioperative, (2) stimulation related or (3) hardware complications (Baizabal Carvallo et al., 2011). Perioperative complications are for example intracranial hemorrhage, stroke, postoperative confusion and vasovagal reactions. Hemorrhage is the greatest risk of DBS surgery, whereby reported incidence rates vary between 0% and 10%, although larger series report rates of ~2% (Goodman & Alterman, 2012). Behavioral changes after DBS may occur in some patients, and include depression, anxiety, hypomania, hypersexuality, apathy, personality changes, and aggression (Farris & Giroux, 2011). Regarding cognition, a decline has been reported in movement disorders, especially when cognition was already compromised, as well as cognitive improvement in psychiatric disorders (Bergfeld et al., 2013; Grubert et al., 2011). Finally, several hardware related side effects exist, whereby infections form the greatest risk and are reported to occur in 8% of patients (Piacentino et al., 2011). Other hardware related complications are battery depletion, sudden battery failure, skin erosion, scar tissue adhesions, migration or breakage of the brain wire or misplaced electrodes (Farris & Giroux, 2011).

*History of deep brain stimulation*

Before the 1950s no psychotropic medication was available yet, and biological treatment strategies for psychiatric disorders were targeted at rather broad forms of putative dysfunction, for example malarial pyrotherapy, hypoglycemic coma or electroconvulsive therapy (Holtzheimer & Mayberg, 2011). Gradually, models about functional and structural neuroanatomy of mood and behavior regulation emerged, and abnormalities were assumed to be caused by dysfunctional thalamo-cortical communication (Moniz, 1937). It was hypothesized that the connections in this network had to be disrupted in order to treat these behavior abnormalities. In 1937, Moniz first described a neurosurgical technique that he called prefrontal leucotomy, later known as frontal lobotomy, in which the connection between the prefrontal lobes and other parts of the brain were disrupted in patients suffering from mental disorders.

In 1947, Spiegel and colleagues helped improving this technique by the invention of a stereotaxic apparatus for the human brain (Hariz et al., 2010; Spiegel et al., 1947), which could be used to make more precise lesions, for example in the medial nucleus of the thalamus. Because of improved neuroanatomical precision, stereotactic neurosurgery drastically replaced the technique of frontal lobotomy. Despite these improvements in the 1950s, stereotactic techniques were not applied often, because at the same time neuroleptic drugs were introduced for mental disorders and the pharmacotherapy for movement disorders improved. The next three decades, the use of stereotactic neurosurgery continued in a limited fashion (Spiegel, 1950). In the 1980s and 1990s it became clear not every patient responded well to pharmacological treatments, as symptoms often remained or severe side effects were experienced. Additionally, more knowledge was gained regarding neural pathophysiology and techniques improved, which led to an increase of stereotaxy use in movement disorders (Lozano & Lipsman, 2013).

Parallel with the introduction of human stereotaxy, the effects of electrodes in the brain were explored and advantages such as its reversible nature were rapidly recognized (see for a clear historical review Hariz et al., 2010). In the 1940s and 1950s, electrodes were implanted in brains of laboratory animals after which behavioral changes were studied (Delgado & Livingston, 1948; Olds & Milner, 1954). The first ideas about the use of electrodes in human brains arose around the same time, focusing on pain disorders and epilepsy. For example, to explore and identify epileptic foci, electrodes were implanted for recording and stimulation. Subsequently, chronic stimulation was introduced as a treatment for epilepsy (Hariz et al., 2010).

Gradually, the first experiments of chronically stimulation of subcortical structures in humans were conducted. Delgado and colleagues wrote in 1952 that electrode implantation could be a possible treatment for psychoticism in humans (Delgado et al., 1952). Real experimental research was first done in patients with neuropsychiatric disorders (Bishop et al., 1963; Heath, 1971; Heath et al., 1955). Treatments of pain disorders with DBS were described in 1975, whereby electrodes were implanted in the somatosensory thalamus of patients (Mazars, 1975). In these days DBS was a new, experimental method, and researchers tried to investigate how to use the electrical stimulation effectively in a safe way. Heath wrote in 1954 how they systematically experimented with electrodes in the brain of schizophrenic patients. Focus was partly on treatment, but also on understanding working mechanisms in the brain, learning from recordings that could be made with the electrodes. Technical issues were investigated whereby electrodes were kept in the brain for longer periods, they were placed more accurately and recordings became more effective. Optimization of wave properties, stimulation duration and other parameter settings was done by trial and error, and experimenting went on.

The foundations of the modern form of DBS were laid in 1987, when Benabid and colleagues at the University of Grenoble, France, published on thalamic DBS to reduce tremor in patients with extrapyramidal movement disorders. Previously, the thalamic nucleus was surgically lesioned in such cases. By using chronic high frequency stimulation, the tremor was stopped and little side effects occurred (Benabid et al., 1987). In 1997 the Food and Drug Administration gave approval to use thalamic DBS in tremor, which almost completely replaced ablative lesioning of the thalamus (Benabid et al., 1996).

Another important development regarding DBS was the discovery of the subthalamic nucleus (STN) as a target in Parkinson’s disease (PD) (Krack et al., 2010). This target was discovered thanks to the the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkey model of PD. Imaging studies in this monkey showed there was increased neuronal activity in the STN (Mitchel et al., 1989). Lesioning this structure reduced all of the major motor disturbances in the contralateral limbs (Bergman et al., 1990). Applying DBS at this specific target in the MPTP monkey resulted in the same clinical outcome (Benazzouz et al., 1993). The next step was to apply DBS at the STN in humans with PD, which also effectively reduced symptoms (Limousin et al., 1995). The STN and globus pallidus internus (GPi) were approved as a target for PD in 2003.

Observations of PD patients whereby comorbid OCD alleviated during DBS treatment indicated that DBS could be a treatment for psychiatric disorders as well. The experimental use of DBS in psychiatric disorders increased rapidly after 1999, when Nuttin and colleagues described the treatment of four patients with OCD by applying chronic, high-frequency stimulation (Nuttin et al., 1999). In 2009, DBS for OCD was officially approved in the United States. Furthermore, DBS was introduced for TS (Vandewalle et al., 1999). Meanwhile, structural and functional imaging techniques, including fMRI, positron emission tomography (PET) and diffusion tensor imaging (DTI), developed rapidly and improved fast, supporting the search for potential new DBS targets.

*Mechanisms of DBS*

Despite the emerging therapeutic application of DBS, its underlying mechanisms of action are far from understood. At the start, DBS was assumed to cause a ‘reversible lesion’, because effective DBS targets mirrored those used for stereotactic lesioning. Although it is now known that stimulating a specific target modulates neural function of broader networks, it is still unclear how this modulation exactly works. The complexity of unraveling the mechanisms of action of DBS arises from the fact that multiple aspects are involved. First of all, DBS is a rather broad term for several kinds of electrical stimulation in the brain. Together with the variability in physical properties of the electrodes, parameters such as frequency, amplitude, pulse width and duration add up to the multiple possible stimulation settings of DBS. Furthermore, different brain areas are used as a target for DBS, depending on the disorder that is treated. Finally, on a cellular level, research suggests that the effects of DBS may depend on the stimulated neural elements (cell bodies, dendrites, or axons), the released molecules (e.g. neurotransmitters, ions, or neurotrophins) and the local synaptic arrangements.

In this section, the basic principles of electrical stimulation on different neural elements will be described together with the influence of their geometric configurations. Furthermore, the discussion regarding effects of DBS on a cellular level will be pointed out, whereby different hypotheses for both inhibitory and excitatory effects of DBS are listed. The main approach is to describe mechanisms of action underlying DBS from a whole network approach.

*Basic principles of stimulating neural elements* The physiological properties of the brain tissue determine the electrical properties, which depend on the specific target elements such as the cell bodies, dendrites or large- or small-diameter axons. Additional factors such as the geometrical configurations play a role in outcome of DBS stimulation.

First of all, the electrical properties and anatomy of the neural elements are important factors. The resistivity of the brain tissue determines what relationship between stimulus amplitude and duration is needed to obtain constant electrical stimulation. The amount of current that is necessary to stimulate a target with long stimulus duration is called “rheobase”. The “chronaxie” is the strength-duration time constant, which is the minimal time duration needed to excite a neural element when the double rheobase intensity is used (Ranck, 1975). Chronaxies vary for each different nerve type; the chronaxies of large myelinated axons are approximately 30 to 200 µs whereas those of cell bodies and dendrites range from 1 to 10 ms (Holsheimer et al., 2000). Since the myelinated axons are the most excitable neural elements, it is likely that these are being stimulated first. This also explains how DBS can modulate the activity of both local and distal neural structures (Kringelbach et al., 2010; Ranck, 1975).

Other important factors that influence the effects of stimulation are the distance and orientation of the neural elements in relation to the electrodes. For example, in monopolar extracellular stimulation, an outward direction of the current causes depolarization while an inward current causes hyperpolarization. Action potentials at depolarized sites can travel through hyperpolarized sites, if not too large. This implicates that, paradoxically, action potentials in axons near the stimulating electrode were current density is highest, can be blocked, while neural elements further away may be stimulated (Ranck, 1975).

*DBS mechanisms of action* Most of the studies describing mechanisms of action on a cellular level were performed with PD patients. An advantage of studying DBS in movement disorders is that symptoms, such as tremor, can reduce directly after stimulation. This makes it easy to relate symptom relief to effects of electrical stimulation. For instance, it was shown that a decrease in the activity of the stimulated neurons corresponds with the effect of decreasing PD symptoms (Kuhn et al., 2010).

An ongoing topic of debate is whether DBS induces activation or inhibition at a neural level (McIntyre et al., 2004). Based on this discussion, four hypotheses are suggested in the literature to explain underlying mechanisms of DBS. The first mechanism regards (1) depolarization blockade, which was studied by Beurrier and colleagues (2001) by using patch-clamp techniques in rat STN slices in vitro. The spontaneous activity of neurons reduced after stimulation, which was thought to be mediated by a reduction of Na+ and Ca2+ voltage-gated currents (Beurrier et al., 2001). The second theory suggests DBS causes (2) synaptic inhibition or activation, via release of inhibitory or excitatory neurotransmitters. For example, local effects of stimulation were measured with microelectrodes in the GPi, which was stimulated to treat PD (Dostrovsky et al., 2000). Stimulation excited the axon terminals of neurons that released GABA and consequently inhibited the target neurons in the GPi. Distal recordings were made in another patient in whom the GPi was stimulated, whereby some of the motor thalamic cells were also inhibited (Pralong et al., 2003). A third possible mechanism of action is that stimulation of efferent axons causes (3) synaptic depression, whereby transmission is inhibited by exhaustion of the neurotransmitters (Urbano et al., 2002). Finally, theories exist whereby DBS is thought to work through (4) stimulation-induced disruption of pathological network activity (McIntyre et al., 2004). Depending on the axon terminals of the stimulated axons, both excitatory and inhibitory effects on the postsynaptic neurons could occur (Lozano & Lipsman, 2013; McIntyre & Hahn, 2010). This approach is not new; Benabid introduced this idea already and postulated that DBS might act by “jamming” pathological network activity (Benabid et al., 1996). In this perspective, psychiatric disorders can be seen as disorders of a specific brain network. The current theory is that DBS restores network function by overriding pathological oscillatory patterns between key brain regions (Kringelbach, 2010; McIntyre & Hahn, 2010).

Functional imaging methods can be used to study global changes elicited by DBS. The most used neuroimaging techniques are PET and fMRI, whereby indirect changes of neural activity are measured. In a PET scan, a radionuclide is induced that emits pairs of gamma rays. A range of activities including blood flow, blood volume, oxygen usage and glucose metabolism can be investigated. In fMRI, the level of oxygen in the cerebral blood is measured. The hemodynamic response consists of the blood oxygen level dependent (BOLD) signal, which is a rapid increase of blood-oxygenation. Despite the fact that it is not exactly known how or why blood flow increases during neuronal activation, the BOLD signal correlates with the local field potentials of neurons, which reflect changes in neural input (Logothetis, 2001; Raichle, 2001). More recently it was shown by using the technology of optogenetics, that specific stimulation of modulated neurons elicits positive BOLD signals (Lee et al., 2010). Both methods are not without health risks in combination with DBS. In PET, the ionized radiation can be a risk whereas in fMRI the magnetic fields can interfere with the active pulse generators and DBS electrodes. Despite these risks, both techniques have been used to study the effects of DBS.

In the following sections, structural and functional abnormalities in the brains of patients with certain psychiatric disorders will be outlined. Then, effects of DBS throughout the brain of these patients will be described in order to reveal changes in underlying pathological circuits and possible similarities between several psychiatric disorders.

**Obsessive-compulsive disorder**

OCD is an anxiety disorder that is characterized by obsessions (chronic, intrusive thoughts) and/or compulsions (repetitive behaviors). These obsessions or compulsions cause distress, are time consuming, or interfere with the person’s life (DSM-IV-TR). Life-time prevalence of OCD of the general population is about 1% to 3% (Ruscio et al., 2010). Standard treatments are psychotherapy, cognitive behavioral therapy or medical treatment with selective serotonin reuptake inhibitors (SSRI). Despite optimizing treatment by combining behavioral and medical approaches, a substantial amount of the OCD patients does not respond to these therapies (Denys, 2006; Kim et al., 2011; Skoog & Skoog, 1999). Patients with severe, refractory OCD are still occasionally treated with ablative neurosurgical techniques, including anterior capsulotomy, anterior cingulotomy, subcaudate tractotomy and limbic leucotomy (Greenberg et al., 2010b). Data about these surgeries suggest many patients benefit (ranging from 35%-70%), although methodological limitations such as low number of patients or no randomized controlled designs have to be taken into account (Greenberg et al., 2003). Related to the relatively large clinical experience with stereotaxy for OCD, this was also the first psychiatric disorder that was tried for DBS (Nuttin et al., 1999). Since then, more than 100 OCD patients have been treated with DBS and promising results are reported (de Koning et al., 2011).

|  |
| --- |
| **Figure 3.** Simplified illustration of cortico-striato-thalamic (CST) loops. Brain structures that exhibited hyper- or hypoactivation in the meta-analysis of Brem et al. (2012) across OCD patients are labelled by arrows pointing upwards (hyperactivation) or downwards (hypoactivation). ACC, anterior cingulate cortex, aINS, anterior insula, dlPFC, dorsolateral prefrontal cortex, IPL, inferior parietal lobule, OFC, orbitofrontal cortex, vmPFC, ventromedial prefrontal cortex. Figure and (part of the) description derived from Brem et al., 2012. |

Another reason for the wide application of DBS for OCD is the availability of a relatively large body of neuroimaging evidence pointing towards well-defined dysfunctional circuits in OCD that can be targeted with DBS. The network that is hypothesized to be involved in OCD pathology is the cortical-striatal-thalamic-cortical circuit (CSTC) (see Figure 3; Menzies et al, 2008; Mian et al., 2010; Radua et al., 2010; Whiteside et al., 2004). Projections in this circuit run from the ventral prefrontal cortex (ventral PFC; including the orbitofrontal cortex (OFC) and ventromedial PFC) and the anterior cingulate cortex (ACC) to the ventral striatum (VS; including the nucleus accumbens (NAc)), or from the dorsolateral PFC and the ACC to the dorsal striatum (including the caudate nucleus and the lenticular nucleus) (Brem et al., 2012, van den Heuvel et al., 2010; Milad & Rauch, 2012).

The OFC, ACC and basal ganglia are likely to play a role in OCD symptoms. The involvement of the OFC in OCD could be explained by its function. Implications after lesion studies suggest the OFC is important for emotional and motivational aspects of behavior, since problems with appropriate affect, inhibition and decision-making are observed (Menzies et al., 2008). This relates to OCD, in which symptoms are related to cognitive and behavioral inflexibility. Structural and functional imaging studies support involvement of the OFC in OCD. In OCD patients decreased gray matter volumes in the OFC are observed (Menzies et al., 2008; Peng et al., 2012; Radua et al., 2010). Additionally, functional imaging studies using fMRI, PET or single-photon emission computed tomography (SPECT) indicate that abnormal activity in the OFC is one of the core features in OCD, independent from particular symptom dimensions (Menzies et al., 2008). Hyperactivity in the OFC is seen during resting state, whereby a positive correlation exists with the severity of OCD symptoms (Holzschneider & Mulert 2011; Hou et al., 2012). Studies whereby symptoms are provoked also show increased activation in the OFC (Borairi & Dougherty, 2011; Lagemann et al., 2012). Other structures that are involved in OCD include the ACC, whereby abnormalities such as a decrease in gray matter volume together with an increase of activation are observed. The ACC is important for response inhibition, which is disturbed in OCD patients and relates to compulsive behaviors.

The basal ganglia are thought to be important in the onset of the repetitive compulsive behaviors that are typical for OCD (Figee et al., 2013). In these structures, increased gray matter is in particular observed in the caudate nucleus and lenticular nucleus (Menzies et al., 2008; Peng et al., 2012; Radua et al., 2010), whereby the increase is correlated with the severity of OCD symptoms (Radua & Mataix-Cols, 2009). Additionally, symptom-provoked and resting-state hyperactivity is seen in the head of the caudate nucleus, a structure that is involved in habits and cognitive rules. Hyperactivity of the caudate nucleus is therefore likely involved in excessive habit formation, which is typical for OCD. These changes go together with structural abnormalities and a decrease of activation in the cerebellum and parietal lobes, which are important for motor coordination and motor inhibition (Borairi & Dougherty, 2011; Holzschneider & Mulert 2011; Hou et al., 2012; Menzies et al., 2008; Whiteside, 2004). In OCD patients this can be related to the decreased inhibition of execution of compulsions. Finally, dysfunctional reward processing in the VS has been observed in OCD, which could indicate that patients are excessively engaged in compulsive behaviors because of its rewarding anxiety-relieving effects (Figee et al., 2011).

Involvement of the mentioned structures in OCD is confirmed by changes following successful medical treatment with SSRIs or cognitive behavioral therapy, whereby decreased activation is observed in the OFC, middle frontal gyrus and temporal regions, together with increased activation in the cerebellum and parietal lobes (Nabeyama et al., 2008). Finally, DTI studies confirm white matter tract changes of the CSTC circuitry in OCD patients, abnormalities are reported in the ACC, cingulum bundle, anterior limb of the internal capsule (ALIC) and corpus callosum (Ayling et al., 2012; Lopez et al., 2013).

The OFC, striatum and thalamus are connected via direct and indirect pathways (van den Heuvel et al., 2010). The direct pathway has an excitatory output effect and projects via the GPi to the thalamus. The indirect pathway has an inhibitory effect and projects via the external part of the globus pallidus and the STN to the thalamus (Brem et al., 2012, Milad & Rauch, 2012). Activation of indirect and direct pathways result in respectively increased or decreased inhibition of the thalamus and increased or decreased excitation of the PFC (van den Heuvel et al., 2010). An imbalance of activity in the direct and indirect pathways probably leads to insufficient inhibition of obsessions and compulsions, which results in typical OCD symptoms. This idea is supported by findings regarding the abnormal functional coupling between the CSTC nodes in OCD patients. A robust finding is increased connectivity between the OFC and VS, whereby the strength correlates with severity of illness (Harrison, 2009; 2013). Furthermore, reduced connectivity between the ventral caudate and insular cortex, as well as between the dorsal caudate and dorsolateral prefrontal and parietal cortices is seen (Harrison, 2013).

To summarize, anatomical changes in OCD patients are observed in the OFC, ACC and basal ganglia, which are part of the CSTC circuit. DTI and functional coupling studies have shown that connections between these nodes are disrupted, and functional abnormalities in the OFC and other brain areas in the CSTC circuit are observed. The OFC, ACC and basal ganglia are important in regulating behavior and cognition, which is disturbed by imbalance of activity in the direct and indirect pathways, resulting in insufficient inhibition of obsessions and compulsions.

*DBS targets and neuroimaging for OCD*

Current targets for treatment-refractory OCD are all part of the CSTC network: the ALIC, the VS/ventral [anterior internal] capsule (VS/VC), the NAc, the STN and the inferior thalamic penduncle (ITP). In this section the effectiveness of DBS in OCD patients is briefly mentioned, by listing the mean improvement and the responder rates (defined as a symptom reduction of >35%) for each target, derived from reviews and recent studies. More important, results from imaging studies are described in order to understand how DBS modulates the disrupted brain networks.

*ALIC & VC/VS* The first DBS target that was used to treat OCD is the ALIC, which was stimulated in four patients by Nuttin and colleagues (1999). In three of these patients symptom reduction was reported. Gradually, the ventral ALIC and adjacent VS became new DBS targets, which were referred to as the VC/VS. Benefit of DBS targeting the ALIC or the VC/VS was reported in several studies (Abelson et al., 2005; Anderson & Ahmed, 2003). In a review of Greenberg and colleagues (2010a) results of DBS targeting the VC/VS in 26 patients from different studies were described. Symptom reduction and functional improvement was seen in 61.5% of the patients, with a responder rate of 38%. Better results were obtained when the electrodes were sited more posterior to the junction of the anterior capsule and the anterior commissure. Corresponding results were described in a more recent study, whereby four out of six patients responded to VC/VS DBS (Goodman et al., 2010).

In a study of Nuttin and colleagues (2003), functional imaging was used to investigate the effects of DBS throughout the brain. Bilateral stimulation of the ALIC was applied in four OCD patients. One patient underwent fMRI ten days postoperatively and showed increased activity in the pons and striatum, and to a lesser extent in the right frontal cortex, superior and middle temporal gyrus and lateral occipital cortex. In three patients PET scans were made three months postoperatively, and reduced frontal activity was observed (Nuttin et al., 2003). Abelson and colleagues (2005) investigated three patients using PET, after bilateral ALIC stimulation. They compared PET recorded activity after operational implantation but before stimulation with activity after three to six weeks of stimulation. In two patients who had positive responses, a decrease in metabolic activity in the OFC was seen. In the patient who failed to respond no change was observed (Abelson et al., 2005). PET was also used in a study of Van Laere and colleagues (2006), whereby five patients received bilaterally DBS in the ALIC and one patient only at the right ALIC. Activity before the operation was compared with healthy controls whereby a reduced resting metabolism in the ventral PFC, motor cortex, dorsal ACC and left inferior parietal cortex was seen. Furthermore, an increase in metabolism in the cerebellum and left VS was observed. On average ten months postoperatively, comparisons between the on-, and off-stimulation conditions within patients were made. Decreased activity in the subgenual ACC, right dorsolateral PFC and right anterior insula was seen, together with an increase in motor cortex activity. A trend towards an activity decrease in the mediodorsal nucleus of the thalamus was described. Finally, the activity in the VS and amygdala increased to a normal level. A reduction in symptoms correlated negatively with a decrease in metabolism in the left and right striata, left hippocampus and left posterior cingulate. The left amygdala and left head of the caudate showed a trend toward a decrease with reduction in symptoms (Van Laere et al., 2006). Rauch and colleagues (2006) compared PET measurements after high frequency DBS targeting the VC/VS with measurements after low frequency stimulation or no stimulation. Six patients were included, whereby measurements were done at least six weeks after recovery from operation. No difference in activity was observed between the low frequency stimulation and no stimulation condition. Comparing high frequency stimulation with these conditions revealed that activation increased in the OFC, ACC, putamen, globus pallidus and thalamus. No significant correlation existed between symptom reduction and magnitude of PET activation (Rauch et al., 2006). In a case study, alterations in activation patterns due to stimulation at contact sides in either the ALIC or VC/VS were studied using fMRI two days postoperative (Baker et al., 2007). Stimulation of the electrode in the ALIC resulted in activation in the middle frontal gyrus, ipsilateral medial thalamus, ACC, head of the caudate nucleus, and globus pallidus. Stimulation of the electrode in the VC/VS resulted in activation in the ipsilateral medial thalamus, head of the caudate nucleus, posterior cingulate cortex and superior, middle, and inferior frontal gyrus (Baker et al., 2007).

To summarize, mapping of functional changes after DBS stimulation of the ALIC and VC/VS learns that activity of structures in the CSTC circuitry are altered. Both increase and decrease of activation are described in structures within this network, such as the OFC, striatum, basal ganglia and thalamus. The ALIC includes fibers linking the OFC to the thalamus, and DBS possibly interrupts these connections leading to a decrease in OFC activity, which is thought to play an important role in the stereotypic behavior seen in OCD (Figee et al., 2013).

*NAc* The NAc forms the main part of the VS and is thought to play an important role in several functions including reward, motivation, addiction and fear. Bilateral and unilateral NAc DBS studies report different results; in bilateral stimulation an average symptom improvement of 51% with a responder rate of 11 out of 19 patients is reported, while unilateral right-sided DBS resulted in a total of only 21% symptom improvement with a responder rate of one out of ten patients (Huff et al., 2010).

Figee and colleagues (2013) recently investigated the NAc-frontal network modulation of bilateral NAc DBS in 16 OCD patients, using fMRI and electroencephalogram (EEG; Denys et al., 2010; Figee et al., 2013). Brain activity of OCD patients during off-stimulation compared with brain activity of healthy subjects showed lower NAc activity and higher connectivity between the NAc and lateral PFC and medial PFC. DBS normalized NAc activity and decreased the excessive frontostriatal connectivity. Furthermore, EEG measurements were done during a symptom-provoking task, whereby DBS attenuated the increase in low-frequency EEG oscillations over the frontal cortex. These findings are in line with the hypotheses that DBS overrides disruptive oscillatory patterns and restores network function (Kringelbach, 2010; McIntyre & Hahn, 2010). Normalization of the synchronization between the NAc and frontal cortices could take place by antidromic stimulation of fibers in the ventral internal capsule that connect the medial PFC with the NAc, or indirectly by stimulation of corticothalamic pathways (Figee et al., 2013).

*STN*  The STN is part of the basal ganglia and was first used as a DBS target in PD, as it is associated with motor behavior. However, it was observed that OCD traits that were present in patients with PD decreased after STN DBS, which motivated researchers to target the STN for OCD as well (Mallet et al., 2002; Fontaine et al., 2004). In a study with 16 OCD patients STN DBS was applied, resulting in a 31% symptom improvement and a responder rate of 12 out of 16 patients, although responders were defined by a 25% symptom reduction instead of 35% (Mallet et al., 2008).

In 2010, Le Jeune and colleagues studied the effects of STN DBS in the brain by making PET scans of ten OCD patients, both during on- and off-stimulation. During off-stimulation, patients showed an increase of activation in the right frontal middle and superior gyri, right parietal lobe, postcentral gyrus, and bilateral putamen compared with healthy control subjects. During on-stimulation, a decrease in activation was observed in the left cingulate gyrus and the left frontal medial gyrus (Le Jeune et al., 2010). Possibly STN DBS is effective by normalizing frontal hyperactivity through the indirect inhibitory CSTC pathway (Figee et al., 2012).

*ITP* The ITP is a fiber bundle that emerges from the anterior part of the thalamus, whereby many fibers are bidirectional connected with the OFC. Only one study used the bilateral ITP as a DBS target, whereby six OCD patients and one MDD patient were treated. The OCD patients showed a symptom improvement of 51% (Jiménez et al., 2012). ITP DBS is thought to reduce OCD symptoms by alteration of OFC activity, but no functional imaging studies were conducted regarding ITP DBS in humans.

To summarize, the disrupted compulsivity circuit in OCD can be modulated at multiple targets, including the ALIC, VC/VS, NAc and STN, whereby synchronization between striatum and frontal cortices appears to normalize and OFC hyperactivity reduces. This may cause a shift from compulsive behaviors to goal directed behaviors.

**Major depressive disorder**

Major depressive disorder (MDD) is characterized by depressed mood or a loss of interest or pleasure in daily activities, consistently for a period of two weeks and affecting social, occupational, educational or other important functioning. MDD can occur one single episode or can be recurrent (DSM-IV-TR). The lifetime prevalence of MDD is estimated at 16% (Kessler et al., 2003). MDD is treated with antidepressants, such as SSRI’s, tricyclic antidepressants, monoamine oxidase inhibitors, or psychotherapy. However, up to one-third of patients do not benefit from these treatments, and medications with novel mechanisms are investigated. Additionally, electroconvulsive therapy is an effective strategy for refractory MDD and new neurostimulatory interventions are currently explored, including repetitive transcranial magnetic stimulation, vagus nerve stimulation, and DBS.

Many neuroimaging studies have been conducted to reveal mechanisms involved in MDD. Compared to OCD, the underlying pathology of MDD is less clear, which is in line with the heterogeneous symptomatology. MDD involves brain systems that regulate mood, anxiety, reward processing, motivation, attention, stress responses and neurovegetative function (Price & Drevets, 2012). Dysfunction in many structures is therefore associated with MDD, including the medial PFC and anatomically related limbic, striatal, thalamic and basal forebrain structures (Price & Drevets, 2012). These structures can be anatomically grouped into frontolimbic and limbic corticostriatopallidothalamocortical (CSPTC) circuits (Taghva et al., 2012) (see Figure 4), or functionally into affective-motivational and cognitive networks.

The affective-motivational network consists of the OFC, ACC and VS and its connections with the hippocampus and amygdala. Anatomical and functional abnormalities in these structures have been found in MDD, which may reflect impaired reward learning underlying depressive symptoms such as anhedonia and amotivation (Price & Drevets, 2012). The most common structural findings in MDD are a reduction of volume in the PFC, especially the OFC, and the subgenual ACC (Pandya et al., 2012; Price & Drevets, 2010). MDD has been related to decreased goal- or reward directed behavior which is thought to depend upon dysfunctional PFC input to the VS (Price & Drevets, 2010). Indeed, decreased ventral striatal response to rewards has been demonstrated in MDD (Pizzagalli et al., 2009). Within the cognitive network, decreased activity is observed in the pre- and subgenual parts of the ACC and increased activity in the thalamus (Pandya et al., 2012; Price & Drevets, 2010). These projections are maintained by projections from the hippocampus to the VS. In patients with MDD, decreased volume of the hippocampus has been found (Bora et al., 2012; Price & Drevets, 2012), together with altered functional connectivity between the subgenual ACC and medial temporal lobe, including the hippocampus (Kwaasteniet et al., 2013). Projections from the amygdala to the VS can also interrupt the cognitive responses. Additionally, the amygdala is involved in fear processing by dysfunctional PFC regulations. In the amygdala, both increase and decrease in volume is observed (Drevets et al., 2008; Pandya et al., 2012). Furthermore, in depressive subgroups, increase in activation in the amygdala is reported in the resting state and in response to emotional stimuli (Price & Drevets, 2012). Increased amygdala activity could also be related to the autonomic imbalance in depression through a medial network dysfunction (Price & Drevets, 2012).

In summary, in MDD different brain regions are involved related to affective-motivational and cognitive functions. Motivation and reward related structures such as the ACC and OFC, may be linked to anhedonic symptoms (Anderson et al., 2012; Drevets et al., 2008; Price & Drevets, 2010), and disturbed PFC or amygdala input to the VS may be related to fear and reward regulation (Drevets et al., 2008).



**Figure 4.** CSPTC limbic circuit. Derived from Taghva et al., 2012.

*DBS targets and neuroimaging for MDD*

DBS for MDD is currently in the experimental phase, whereby positive results are reported. The used targets lie within networks that connect limbic, cortical, and subcortical areas, modulating different aspects of MDD (Anderson et al., 2012). Current targets are the VC/VS, NAc, subgenual cingulated gyrus (SCG), medial forebrain bundle (MFB), ITP and lateral habenula (LHb).

*VC/VS* The VC/VS was targeted in 17 patients by Malone and colleagues (2009, 2010), reporting a responder rate of 53% and an average 46% symptom improvement after one year (Malone et al., 2009; 2010). The VC/VS is connected to medial prefrontal regions within the motivational network, and stimulation of the VC/VS may reverse dysfunctional reward processing in MDD (Pizzagalli et al., 2009) by changing activity in this network. Although no functional imaging data of VC/VS DBS in MDD patients are available, effective ventral striatal stimulation for OCD is indeed related to activity changes in the NAc, medial PFC and SCG (Malone, 2010; Figee, 2013).

*NAc* Similar to the VC/VS target, the NAc is part of the VS that is involved in motivational reward processes by receiving and projecting information from and towards prefrontal and limbic structures (Schlaepfer et al., 2008). The NAc could be used as a DBS target for MDD because of its central role in mediating motivational behavior by transmitting information from emotional to motor brain regions. The NAc was targeted with DBS to treat MDD by Schlaepfer and colleagues (2008). In their study, symptom improvement was observed in all three treated patients. The study was extended and eventually five of eleven patients responded to bilateral NAc stimulation with a total symptom reduction of 36%, which lasted over four years (Bewernick et al., 2010; Bewernick et al., 2012). Immediate post-operative PET images of the three first treated patients showed increased activation in the bilateral VS (including the NAc), bilateral dorsolateral and dorsomedial PFC and cingulate cortex, and bilateral amygdala. Decreased metabolism was observed in the ventromedial and ventrolateral PFC, dorsal caudate nucleus, and thalamus (Schlaepfer et al., 2008). In seven patients PET scans were made six months after stimulation onset which revealed metabolic changes in prefrontal subregions (including the OFC), SCG, posterior cingulate cortex, thalamus, caudate nucleus and precentral gyrus. It is hypothesized that via anatomical and functional connections of the NAc with other limbic and prefrontal regions the pathological network hyperactivity decreased. Interestingly, the increase in activity in the NAc, which was observed directly after stimulation, was not observed anymore after 6 months of stimulation. Furthermore, a difference in amygdala activity was noted between responders and non-responders. Normalization of amygdala activity may explain reduced anxiety after NAc DBS (Bewernick et al., 2010).

*SCG* SCG stimulation resulted in a responder rate of 32 out of 60 MDD patients after one year (Lozano et al., 2008; 2012; Holtzheimer et al., 2012; Neimet et al., 2008; Puigdemont et al., 2012). The SCG is a central hub between limbic, reward and prefrontal cortical regions. Correspondingly, brain changes after SCG DBS in MDD involve limbic and cortical areas. In the first study using PET imaging in five patients, activity decreases in the subgenual cingulate region and OFC were found after three months of SCG stimulation. After six months of stimulation, activity decreased in the hypothalamus, anterior insula and medial frontal cortex, together with increases in the dorsolateral prefrontal, dorsal anterior and posterior cingulate, premotor and parietal regions (Mayberg et al., 2005). These results were replicated in eight SCG-targeted patients, whereby decreases in orbital and medial frontal cortex and insula and increases in lateral PFC, parietal, anterior midcingulate, and posterior cingulated areas were seen. Finally, metabolic changes were found at the SCG itself (Lozano et al., 2008). In sum, SCG DBS appears to modulate both the affective-motivational and the cognitive network.

*MFB* The newest DBS target for MDD is the MFB, which connects structures from the reward pathway, including the NAc, ventral tegmental area, ventromedial and lateral nuclei of the hypothalamus, and the amygdala. The ventral tegmental area is a central structure of the reward circuit and is connected to the supero-lateral branch of the MFB (Schlaepfer et al., 2013). After 12-33 weeks of MFB DBS, six of seven patients were responders with a total symptom reduction of 36% after 12 weeks. No imaging data of MFB DBS are available.

*ITP* The ITP connects the thalamus with the OFC, which is hyperactive in MDD patients (Jiménez et al., 2012). One MDD patient was treated with ITP DBS in 2005, resulting in reduced depressive symptoms (Jiménez et al., 2005). No functional imaging data were collected for this patient.

*LHb* The habenula is divided in the lateral (LHb) and medial (MHb) portion. The LHb is located on the dorsomedial surface of the caudate thalamus and projects to brainstem nuclei that are involved in the metabolism of dopamine, serotonine and noradrenaline. Furthermore, animal models implicate that the LHb is involved in controlling reward (Sartorius et al., 2010). Two MDD patients were treated using the LHb as a DBS target whereby complete remission was achieved (Sartorius et al., 2010; Schneider et al., 2012). In the first patient, PET imaging was used and an only an increase of metabolism at the electrode tips was reported (Sartorius et al., 2010).

*Other targets (GPi and STN)* Positive effects on mood and co-morbid MDD were observed after stimulating targets for movement disorders. The GPi for example, is a common DBS target for refractory tremor and motor fluctuations in PD. Kosel and colleagues (2007) described how both dyskinesia and comorbid MDD resolved after bilateral GPi DBS. Furthermore, in a study of Campbell and colleagues (2012), STN DBS in PD patients resulted in mood improvement in the majority of participants, which was unrelated to the degree of DBS-induced motor improvement. Both GPi and STN are located within the CSPTC circuit. STN activation influences the GPi directly, and stimulation at either side could possibly normalize frontal hyperactivity, which is seen in MDD.

To summarize, imaging data for DBS targets in MDD are only available for the NAc and SCG. DBS at both targets influences activity of areas within the affective-motivational and cognitive circuits, including the VS, OFC, sgACC and amygdala. By normalizing activity in the VS, OFC and sgACC, DBS of the NAc and SCG may therefore lead to a restored reward learning system enabling improvement of anhedonia and amotivation symptoms of MDD. In addition, normalization of amygdala activity may restore prefrontal emotional control and reverse exaggerated processing of aversive and negative stimuli. In addition, SCG DBS also modulates more posterior cortical areas, which might be beneficial for MDD by restoring cognitive control.

**Tourette syndrome**

TS is a tic disorder with onset before the age of 18, characterized by multiple physical (motor) tics and at least one vocal (phonic) tic. A tic is a sudden, fast, repeated, non-rhythmic, stereotype, motor movement or vocal expression (DSM-IV-TR). Prevalence of TS is estimated at 1% of worldwide population (Robertson, 2012). Comorbid neuropsychiatric disorders occur in approximately 90% of patients, most often attention deficit hyperactivity disorder and OCD (Cavanna et al., 2009). The decision to treat TS depends on the degree of impairment caused by the tics, and often education of patients, family and other involved persons is sufficient. Behavior therapies for TS address the external cues that induce tics, and also the premonitory urge preceding tics. Effective drug treatment involves alpha adrenergic agonists or dopamine D2 antagonists. In some cases, medication does not help or severe side effects occur. Since 1999, DBS is a possible treatment for these refractory TS patients (Vandewalle et al., 1999).

TS is related to dysfunctions in regions involved in habit formation, including the basal ganglia, thalamus, and frontal cortex (Leckman et al., 2010). In TS, disinhibition in the CSTC circuit is assumed to underlie dysfunctional coupling of sensory cues with motor actions. Abnormalities in dopamine neurotransmission within the fronto-striatal circuitry are associated with TS. Recently, a decrease of availability of D2/3 receptors in the striatum were observed in both TS and OCD, which may lead to an increase of dopaminergic activity (Denys et al., 2013). Exaggerated signaling of striatal dopamine will reduce the inhibitory output from the basal ganglia, which can result in the execution of tics (see Figure 5; Piedad et al., 2012). Structural imaging studies and post mortem studies in TS patients show a reduction of caudate volume together with an increase of the hippocampus, amygdala and thalamus (Ganos et al., 2012; Leckman et al., 2010). Furthermore, PFC volumes are larger and in particular the OFC is altered (Draganski et al., 2010; Ganos et al., 2012). The OFC is involved in decision-making and rewards, and alterations could cause deficits in flexible control of behavior (Draganski et al., 2010). Other PFC structures are thought to be involved in behavioral inhibition and controlling impulses. In the right dorsal lateral cortex, which is also important for inhibitory control, cortical thinning was observed (Leckman et al., 2010). Furthermore, enlargement of the putamen and the motor part of the corpus callosum was seen (Ganos et al., 2012).



**Figure 5.** The cortico-striato-thalamo-cortical circuit (CSTC) in Gilles de la Tourette syndrome. Proposed model for CSTC pathways in healthy subjects (A) and in patients with Gilles de la Tourette syndrome (B). There are 2 parallel pathways within the CSTC circuitry. In the direct pathway, striatal outputs project forward via the GPi, whereas in the indirect pathways striatal outputs project to the GPe, STN, and then forward via the GPi. Abnormal DA signaling at the level of the striatum may result in reduced inhibitory output from the basal ganglia, by potentiating GPe inhibition of the GPi. This results in overall disinhibition of the activity of the CSTC circuitry. GPi, internal portion of the globus pallidus; STN, subthalamic nucleus; DA, dopamine; GPe, external portion of the globus pallidus; sharp arrows, excitatory projections; blunt arrows, inhibitory projections. Figure and description derived from Piedad et al., 2012.

DTI studies revealed white matter changes in TS patients in the motor and somatosensory circuits, and fronto-striatal, interhemispheric and transcallosal connections (Draganski et al., 2010; Ganos et al., 2012). Changes in connectivity are also observed in the basal ganglia, thalamus, NAc and amygdala (Ganos et al., 2012). One explanation of amygdala involvement is that emotional experiences that are signaled by the amygdala can affect motor pathways, via projections to the VS, which can influence motor areas in the dorsal striatum (Wang et al., 2011). Interestingly, comparable pathways are involved in addiction, which also has a compulsive component (Wang et al., 2011).

In functional imaging studies in TS, a distinction can be made between motor and sensory systems involved in tic generation, including the sensations prior to tics, and tic execution. The supplementary motor area (SMA) seems to be of particular importance in tic generation. Prior tic onset, the ACC, insular cortex, and parietal operculum have found to be activated. The parietal operculum is involved in sensorimotor integration, attention and learning (Draganski et al., 2010). At tic onset the sensorimotor areas are highly active, during tic performance increased activation is seen in somatosensory and premotor cortex, putamen, amygdala and hippocampus, and decreased activations in caudate nucleus and ACC (Ganos et al., 2012; Leckman et al., 2010; Wang et al., 2011). The latter two structures are part of circuits involved in inhibition of tics or in the sensations that induce them (Wang et al., 2011).

*DBS targets and neuroimaging for TS*

The circuits including the basal ganglia, thalamus and frontal cortex are important for timing and sequencing of movements, which are disturbed in TS. All targets for TS lie within these circuits, the main targets are the thalamus and GPi. In a few studies the ALIC and NAc were used as a target, combined or in isolation, and in one study the STN was targeted (Piedad et al., 2012; Saleh et al., 2012). From 1999 until 2012, about 99 cases were treated with DBS for TS (Piedad et al., 2012).

*Thalamus* The thalamus is the most used target in TS, whereby specifically the intalaminar and midline co-ordinates are stimulated. These structures are associated with several cognitive functions, stress response and arousal, and are connected with the motor and limbic structures (Piedad et al., 2012). In a study with 36 patients, a reduction of 54.2% of symptoms was observed in 19 of them after two years of follow-up (Servello et al., 2009). It is thought that thalamic DBS can normalize the disinhibited activity in the CSTC circuit by reduced thalamic and striatal dopamine activity. This was investigated by making [18F]fallypride PET scans, which can image availability of dopamine (D2/3) receptors as an indirect measure of endogenous dopamine (Vernaleken et al., 2009). An increase of endogenous dopamine in thalamus and striatal areas was found when DBS was turned off, which suggests that thalamic DBS is effective for TS by normalizing excessive dopamine release.

*GPi* Both the posteroventral and anteromedial GPi are used as DBS targets in TS (Martinez-Ferdandez et al., 2011). The anteromedial GPi mediates the output of the basal ganglia to the thalamus, and is involved in motor function and behavior (Cannon et al., 2012). In a study with eleven TS patients, DBS at the anteromedial GPi resulted in 48% reduction in motor tics and 56.5% reduction in phonic tics. In six patients a reduction of more than 50% was seen after three months. It is thought that GPi DBS restores the decreased inhibitory output from the basal ganglia to other structures in the CSTC circuit (Piedad et al., 2012). However, no functional imaging data during GPi DBS are available.

*Other targets (ALIC, NAc, STN)*

In addition to the thalamus and GPi, other targets within the CSTC circuit have been stimulated to treat TS, e.g. ALIC, NAc and STN. Stimulating the NAc or ALIC may reverse hyperactivation of the direct pathway in TS. (Zqbek et al., 2008). Moreover, NAc and ALIC DBS are effective for OCD, which is an indication TS symptoms may be responsive to these targets as well (Piedad et al., 2012). DBS of the STN may be effective for TS by its direct regulatory influence on motor cortical activity and by its function in the indirect frontostriatal network. By its excitatory influence on the GPi, STN DBS may have greater effects on both limbic and sensorimotor circuits, compared to stimulating the GPi or thalamus in isolation (Piedad et al., 2012). No imaging data are available for DBS in any of these alternative targets.

To summarize, all DBS targets for TS lie within the CSTC circuit. Only one DBS study for TS involved imaging data, which revealed that thalamic DBS causes a decrease of dopamine in the thalamus and striatal areas. This fits the hypothesis that inhibitory dopaminergic functions within the CSTC circuit are disrupted in TS, which can be restored with DBS.

**Anorexia Nervosa**

In the DSM-IV eating disorders are divided in three subgroups: AN, bulimia nervosa and eating disorder not otherwise specified (DSM-IV-TR). AN is characterized by a refusal to maintain normal body weight combined with fear of gaining weight and a disturbance in the way in which one’s body weight is experienced. In bulimia nervosa recurrent episodes of binge eating exist followed by inappropriate compensatory behavior in order to prevent weight gain (DSM-IV-TR). Lifetime prevalence is estimated at 4-6% worldwide (Sun & Liu, 2013). Current therapies include family therapy, cognitive behavioral therapy, psychotherapy or medical treatment. Almost half of current patients are treatment refractory (Sun & Liu, 2013). The use of DBS in eating disorders is only used a few times for AN, which will be the main focus of this section.

AN patients experience an abnormal body image and body schema. It is assumed that visual and proprioceptive information are integrated to a body schema within the parietal cortex (Wu et al., 2013). In the brains of AN patients, a global decrease in grey and white matter has been found, specifically decreased volumes of the inferior parietal lobe (Titova et al., 2013), together with abnormal hypometabolism in this structure and the dorsolateral PFC (Pietrini et al., 2011). The inferior parietal lobe is involved in visuo-spatial processing whereas the dorsolateral PFC regulates emotion impulses, which is mediated by limbic structures. Both structures are connected to the parietal cortex.

The reward system is assumed to be altered in AN patients, whereby the restriction of food intake results in abnormal reward responses towards food. Alterations were seen in the hypothalamus that is involved in eating behavior and the metabolism of food. The hypothalamus projects to the NAc, which is important for reward or natural behaviors, including feeding (Sun & Liu, 2013). Another structure that shows hyperactivity in AN patients is the ACC, which is connected to the dorsolateral PFC and inferior parietal lobe. The ACC is involved in identifying and processing emotional significance of stimuli to produce an adequate effective response, which is disturbed in AN patients (Pietrini et al., 2011).

To summarize, in AN patients structural and functional alterations have been found in frontal and parietal areas and hypothalamus. These structures are related to body image and reward, which are disturbed in patients with AN.

*DBS targets and neuroimaging for AN*

The first positive result of DBS for AN was seen in a women who was primarily treated for MDD (Israël et al., 2010). The electrodes were implanted at the SCG. The SCG, as a part of the ACC, is involved in perception of body image and food, which is disturbed in AN patients. A second patient with AN was primarily treated for OCD with DBS at the ALIC and bed nucleus of the stria terminalis, which resulted in remission of AN symptoms (Barbier et al., 2011). The Shanghai group (Wu et al., 2013) treated four AN patients with bilateral NAc DBS, which resulted in an average increase of 65% in body weight. In the most recent study, six AN patients were treated with subcallosal cingulated DBS (Lipsman et al., 2013). In three of six patients, the body-mass index (BMI) was first increased with pre-surgical feeding but then stabilized with DBS to a value that was higher than the BMI at baseline. In this study, PET scans were made six months after DBS treatment. A decrease in metabolism was seen in the ACC and medial frontal gyrus, and an increase in the parietal lobes and insula. Decreased parietal activity in AN patients has been linked to body image alterations and this appears to be reversed by SCG DBS. The insula is part of a fear-anxiety circuit and is involved in sensation of taste and monitoring the internal environment, which may explain why DBS-induced changes of this structure were beneficial for AN patients. Finally, SCG DBS was related to significantly improved mood in all AN patients and it may thus be possible that AN improvement is secondary to changes in mood circuits.

To summarize, only one study used neuroimaging after DBS in AN. SCG DBS modulated parietal and insula activity, which may normalize the body schema of an AN patient. Decreased ACC activity could be responsible for a restored reward system.

**Discussion**

In this review, we explored the neural mechanisms of action of DBS in a variety of mental disorders to gain insights in underlying brain circuits that can be used as new DBS targets. Reviewing imaging data of patients suffering from obsessive-compulsive disorder (OCD), major depressive disorder (MDD), Tourette syndrome (TS) and Anorexia Nervosa (AN) enabled us to identify brain circuits that are linked to overlapping cognitive, affective and motor processes, rather than to existing DSM-IV classifications.

Disrupted inhibitory functions within the CSTC circuitry can cause compulsivity and motor disinhibition, which is seen in both OCD and TS patients. The basal ganglia, including the STN, are part of this circuit and are involved in the onset of repetitive compulsive behavior. Another structure within the CSTC network that is linked to these symptoms is the ACC, which is involved in response inhibition, but also in reward functions. DBS at the STN, NAc, ALIC or VC/VS, all nodes within the CSTC network, can override dysfunctional metabolism and normalize frontal hyperactivity, which results in alleviating of compulsive and repetitive symptoms.

Abnormal size and activity of the OFC and ACC are seen in OCD, MDD, and AN patients. These structures are important for emotional and motivational aspects of behavior and are involved in reward value, whereby alterations could cause anhedonia or reward dysfunction. These functions are all in one way disrupted in the listed psychiatric disorders, whereby differences in expression exist. Normalizing OFC and ACC activity can be achieved by stimulating the NAc, VC/VS and the MFB.

Motor compulsions or motor tics that are seen in OCD and TS are caused by motor disinhibition. DBS of the STN directly influences on motor cortical activity by its function in the indirect frontostriatal network, and can alleviate pathological motor compulsions.

Imbalance between emotional and cognitive circuits can lead to symptoms related to negative emotions. Important structures within the cognitive circuit are the VS and dorsolateral PFC. A dysfunctional affective-motivational circuit is more specifically related to anxiety or depressive mood. These symptoms are related mainly to MDD, but occur frequently in OCD, TS and AN as well. Key structures are the NAc, amygdala and SCG. SCG DBS modulates both the affective-motivational and cognitive networks. The NAc is also important for motivation and fear, and targeting the NAc normalizes its activity together with normalization of frontostriatal connectivity. Furthermore, NAc DBS alters the amygdala, which is related to mood and anxiety.

The assumption that a certain dysfunctional neural circuit can manifest itself in various psychiatric disorders as differentiated by the DSM-IV is confirmed by the observation that most patients suffer from more than one psychiatric disorder. For example, 90% of TS patients have comorbid psychiatric disorders. It is likely that these disorders share underlying pathology, and focusing on the disrupted circuitry will probably be more helpful in treating patients with DBS than remain tied to the DSM-IV label. This idea is supported by the observation that applying DBS in patients with multiple psychiatric disorders often cures more than one of these disorders. The overlap in structural and functional pathology goes even beyond the boundary of psychiatric disorders, which is seen after DBS treatment in patients with motor disorders, whereby recovery of comorbid psychiatric disorders is often reported (e.g. Kosel et al., 2007). The overlap in underlying pathological brain activity between various DSM-IV disorders explains also why a specific target can be stimulated to treat patients with different disorders. Neuroimaging after DBS treatment reveals that brain areas that showed abnormal activity before stimulation tend to normalize when DBS is applied, which is often correlated with a decrease of symptoms. The latter finding is important, since it confirms that a direct relation exists between the abnormal activation in certain structures and observed symptoms. A next step to improve target selection for DBS could be to group patients based on dysfunctional circuits in order to investigate which target within the circuit should be stimulated to have the best results.

**Conclusion**

Neuroimaging studies can lead to a new approach in psychiatry, whereby the current diagnostic classification system can shift completely from purely behavioral observations towards dysfunctional circuits. In this view, symptoms can be described in relation to dysfunctional brain circuits that can be investigated for individual patients using PET or MRI scans. These scans could form the basis of deciding which target would be the most useful for DBS treatment. Although there is ample imaging data that can help defining brain circuits of mental disorders, little is still known about the exact effects of DBS on these circuits. However, general knowledge about what brain areas are affected after stimulating specific targets combined with the identification of specific symptoms in a patient could already provide information regarding the most favorable target for an individual.

**References**

Abelson, J. L., Curtis, G. C., Sagher, O., Albucher, R. C., Harrigan, M., Taylor, S. F., Martis, B., & Giordani, B. (2005). Deep brain stimulation for refractory obsessive-compulsive disorder. *Biological Psychiatry, 57(5),* 510-516.

American Psychiatric Association. (2000). Diagnostic and statistical manual of mental disorders (4th ed., text rev.). Washington, DC: Author.

Anderson, D., & Ahmed, A. (2003). Treatment of patients with intractable obsessive-compulsive disorder with anterior capsular stimulation. Case report. *Journal of Neurosurgery, 98,* 1104-1108.

Anderson, R. J., Frye, M. A., Abulseoud, O. A., Lee, K. H., McGillivray, J. A., Berk, M., & Tye, S. J. (2012). Deep brain stimulation for treatmen-resistant depression: efficacy, safety and mechanisms of action. *Neuroscience and Biobehavioral Reviews, 36*, 1920-1933.

Ayling, E., Aghajani, M., Fouche, J-P., & Wee, van der, N. (2012). Diffusion tensor imaging in anxiety disorders. *Current Psychiatry Reports, 14,* 197-202.

Baizabal Carvallo, J. F., Simpson, R., & Jankovic, J. (2011). Diagnosis and treatment of complications related to deep brain stimulation hardware. *Movement Disorders, 26(8),* 1398-1406.

Baker, K. B., Kopell, B. H., Malone, D., Horenstein, C., Lowe, M., Phillips, M. D., & Rezai, A. R. (2007). Deep brain stimulation for obsessive-compulsive disorder: using functional magnetic resonance imaging and electrophysiological techniques: technical case report. *Neurosurgery, 61,* 367-368.

Barbier, J., Gabriëls, L., Laere, van, K., & Nuttin, B. (2011). Successful anterior capsulotomy in comorbid Anorexia Nervosa and obsessive-compulsive disorder: case report. *Neurosurgery, 69(3),* E745-751.

Benabid, A. L., Pollak, P., Gao, D., Hoffmann, D., Limousin, P., Gay, E., Payen, I., & Benazzouz, A. (1996). Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. *Journal of Neurosurgery, 84,* 203-214.

Benabid, A. L., Pollak, P., Louveau, A., Henry, S., & Rougemont, de, J. (1987). Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. *Applied Neurophysiology, 50*, 344-346.

Benazzouz, A., Gross, C., Féger, J., Boraud, T., & Bioulac, B. (1993). Reversal of rigidity and improvement in motor performance by subthalamic high-frequency stimulation in MPTP-treated monkeys. *European Journal of Neuroscience, 5(4),* 382-389.

Bergfeld, I. O., Mantione, M., Hoogendoorn, M. L. C., & Denys, D. (2013). Cognitive functioning in psychiatric disorders following deep brain stimulation. *Brain Stimulation,* In Press.

Bergman, H., Wichmann, T., & DeLong, M. R. (1990). Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. *Science, 249(4975),* 1436-1438.

Beurrier, C., Bioulac, B., Audin, J., & Hammond, C. (2001). High-frequency stimulation produces a transient blockade of voltage-gated currents in subthalamic neurons. *Journal of Neurophysiology, 85*, 1351-1356.

Bewernick, B. H., Huerlemann, R., Matusch, A., Kayser, S., Grubert, C., Hadrysiewicz, B., . . . Schlaepfer, T. E. (2010). Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. *Biological Psychiatry, 67*, 110-116.

Bewernick, B. H., Kayser, S., Sturm, V., & Schlaepfer, T. E. (2012). Long-term effects of nucleus accumbens deep brain stimulation in treatment-resistant depression: evidence for sustained efficacy. *Neuropsychopharmacology, 37,* 1975-1985.

Bishop, M. P., Elder, S. T., & Heath, R. G. (1963). Intracranial self-stimulation in man. *Science, 140(3565),* 394-396.

Blomstedt, P., Sjöberg, R. L., Hansson, M., Bodlund, O., & Hariz, M. I. (2012). Deep brain stimulation in the treatment of obsessive-compulsive disorder. *World Neurosurgery,* In Press.

Bora, E., Harrison, B. J., Davey, C. G., Yücel, M., & Pantelis, C. (2012). Meta-analysis of volumetric abnormalities in cortico-striatal-pallidal-thalamic circuits in major depressive disorder. *Psychological Medicine, 42*, 671-681.

Borairi, S., & Dougherty, D. D. (2011). The use of neuroimaging to predict treatment response for neurosurgical interventions for treatment-refractory major depression and obsessive-compulsive disorder. *Harvard Review of Psychiatry, 19(3),* 155-161.

Brem, S., Hauser, T. U., Lannaccone, R., Brandeis, D., Drechsler, R., & Walitza, S. (2012). Neuroimaging of cognitive brain function in paediatric obsessive compulsive disorder: a review of literature and preliminary meta-analysis. *Journal of Neural Transmission, 119,* 1425-1448.

Campbell, M. C., Black, K. J., Weaver, P. M., Lugar, H. M., Videen, T. O., Tabbal, S. D., . . . Hershey, T. (2012). Mood response to deep brain stimulation of the subthalamic nucleus in Parkinson's disease. *Journal of Neuropsychiatry and Clinical Neuroscience, 24(1),* 28-36.

Cannon, E., Silburn, P., Coyne, T., O’Maley, K., Crawford, J. D., & Sachdev, P. R. (2012). Deep brain stimulation of anteromedial globus pallidus interna for severe Tourette's syndrome. *American Journal of Psychiatry, 169(8),* 860-866.

Cavanna, A. E., Servo, S., Monaco, F., & Robertson, M. M. (2009). The behavioral spectrum of Gilles de la Tourette syndrome*. Journal of Neuropsychiatry and Clinical Neurosciences, 21(1),* 13-23.

Delgado, J. M., Hamlin, H., & Chapman, W. P. (1952). Technique of intracranial electrode implacement for recording and stimulation and its possible therapeutic value in psychotic patients. *Confinia Neurologica, 12,* 315-319.

Delgado, J. M., & Livingston, R. B. (1948). Some respiratory, vascular and thermal responses to stimulation of orbital surface of frontal lobe. *Journal of Neurophysiology, 11,* 39-55.

Denys, D. (2006). Pharmacotherapy of obsessive-compulsive disorder and obsessive-compulsive spectrum disorders. *Psychiatric Clinics of North America. 29(2),* 553-584.

Denys, D., Mantione, M., Figee, M., Munckhof, van den, P., Koerselman, F., Westenberg, H., Bosch, A., & Schuurman, R. (2010). Deep brain stimulation of the nucleus accumbens for treatment refractory obsessive-compulsive disorder. *Archives of General Psychiatry, 67(10),* 1061-1068.

Denys, D., De Vries, F., Cath, D., Figee, M., Vulink, N., Veltman, D. J., . . . , Van Berckel, B. N. M. (2013). Dopaminergic activity in Tourette syndrome and obsessive-compulsive disorder. European Neuropsychopharmacology. In Press.

Dostrovsky, J. O., Levy, R., Wu, J. P., Hutchison, W. D., Tasker, R. R., & Lozano, A. M. (2000). Microstimulation-induced inhibition of neuronal firing in human globus pallidus. *Journal of Neurophysiology, 84(1),* 570-574.

Draganski, B., Martino, D., Cavanna, A. E., Hutton, C., Orth, M., Robertson, M. M., Critchley, H. D., & Frackowiak, R. S. (2010). Multispectral brain morphometry in Tourette syndrome persisting into adulthood. *Brain, 133,* 3661-3675.

Drevets, W. C., Price, J. L., & Furey, M. L. (2008). Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Structure and Function, 213,* 93-118.

Farris, S., & Giroux, M. (2011). Deep brain stimulation: a review of the procedure and the complications. *Journal of the American Academy of Physician Assistants, 24(2),* 39-42.

Figee, M., Luigjes, J., Smolders, R., Valencia-Alfonso, C., Wingen, van, G., Kwaasteniet, de, B., . . . Denys, D. (2013). Deep brain stimulation restores frontostriatal network activity in obsessive-compulsive disorder. *Nature Neuroscience, 16(4),* 386-389.

Figee, M., Munckhof, van den, P., Schuurman, R., & Denys, D. Neuroimaging deep brain stimulation in psychiatric disorders. In: Deep Brain Stimulation: A New Frontier in Psychiatry. Denys, D. Feenstra, M., & Schuurman, R. (eds). Berlin; Heidelberg: Springer; 2012.

Figee, M., Vink, M., Geus, de, F., Vulink, N., Veltman, D. J., Westenberg, H., & Denys, D. (2011). Dysfunctional reward circuitry in obsessive-compulsive disorder. *Biological Psychiatry, 69,* 867-874.

Fontaine, D., Mattei, V., Borg, M., Langsdorff, von, D., Magnie, M-N., Chanalet, S., Robert, P., & Paquis, P. (2004). Effect of subthalamic nucleus stimulation on obsessive-compulsive disorder in a patient with Parkinson disease. *Journal of Neurosurgery, 100,* 1084-1086.

Ganos, C., Roessner, V., & Münchau, A. (2012). The functional anatomy of Gilles de la Tourette syndrome. *Neuroscience and Biobehavioral Reviews.* In Press.

Goodman, W. K., & Alterman, R. L. (2012). Deep brain stimulation for intractable psychiatric disorders. *Annual Review of Medicine, 63,* 511-524.

Goodman, W. K., Foote, K. D., Greenberg, B. D., Ricciuti, N., Bauer, R., Ward, H., Shapira, N. A., Wu, S. S., . . . Okun, M. S. (2010). Deep brain stimulation for intractable obsessive compulsive disorder: pilot study using a blinded, staggered-onset design. *Biological Psychiatry, 67,* 535-542.

Greenberg, B. D., Gabriels, L. A., Malone, D. A., Rezai, A. R., Friehs, G. M., Okun, M. S., . . . Nuttin, B. J. (2010). Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: worldwide experience. *Molecular Psychiatry, 15,* 64-79.

Greenberg, B. D., Price, L. H., Rauch, S. L., Friehs, G., Noren, G., Malone, D., . . . Rasmussen, S. A. (2003). Neurosurgery for intractable obsessive-compulsive disorder and depression: critical issues. *Neurosurgery Clinics of North America, 14(2),* 199-212.

Greenberg, B. D., Rauch, S. L., & Haber, S. N. (2010). Invasive circuitry-based neurotherapeutics: stereotactic ablation and deep brain stimulation for OCD. *Neuropsychopharmacology, 35,* 317-336.

Grubert, C., Hurlemann, R., Bewernick, B. H., Kayser, S., Hadrysiewicz, B., Axmacher, N., Sturm, V., & Schlaepfer, T. E. (2011). Neuropsychological safety of nucleus accumbens deep brain stimulation for major depression effects of 12-month stimulation. *The World Journal of Biological Psychiatry, 12,* 516-527.

Hariz, M. I., Blomstedt, P., & Zrinzo, L. (2010). Deep brain stimulation between 1947 and 1987: the untold story. *Neurosurgical focus, 29(2),* E1.

Harrison, B. J., Pujol, J., Cardoner, N., Deus, J., Alonso, P., López-Solà, M., . . . Soriano-Mas, C. (2013). Brain corticostriatal systems and the major clinical symptom dimensions of obsessive-compulsive disorder. *Biological Psychiatry, 73,* 321-328.

Harrison, B. J., Soriano-Mas, C., Pujol, J., Ortiz, H., López-Solà, M., Hernández-Ribas, . . . Cardoner, N. (2009). Altered corticostriatal functional connectivity in obsessive-compulsive disorder. *Archives of General Psychiatry, 66(11),* 1189-1200.

Heath, R. G. (1971). Depth recording and stimulation studies in patients. In A. Winter (Ed), *The surgical control of behavior* (pp. 21-37). Springfield, Illinois.

Heath, R. G. (Ed). 1954. Studies in schizophrenia. Cambridge, Mass.: Harvard University Press. pp. 42-47.

Heath, R. G., Monroe, R. R., & Mickle, W. A. (1955). Stimulation of the amygdaloid nucleus in a schizophrenic patient. *American Journal of Psychiatry, 111,* 862-863.

Heuvel, van den, O. A., Werf, van der, Y. D., Verhoef, K. M. W., Wit, de, S., Berendse, H. W., Wolters, E. C., Veltman, D. J., & Groenewegen, H. J. (2010). Frontal-striatal abnormalities underlying behaviors in the compulsive-impulsive spectrum. *Journal of the Neurological Sciences, 289,* 55-59.

Holsheimer, J., Demeulemeester, H., Nuttin, B., & Sutter, de, P. (2000). Identification of the target neuronal elements in electrical deep brain stimulation. *European Journal of Neuroscience, 12,* 4573-4577.

Holtzheimer, P. E., Kelley, M. E., Gross, R. E., Filkowski, M. M., Garlow, S. J., Barrocas, A., . . . Mayberg, H. S. (2012). Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. *Archives of General Psychiatry, 69(2),* 150-158.

Holtzheimer, P. E., & Mayberg, H. S. (2011). Deep brain stimulation for psychiatric disorders. *The Annual Review of Neuroscience, 34,* 289-307.

Holzschneider, K., & Mulert, C. (2011). Neuroimaging in anxiety disorders. *Dialogues in Clinical Neuroscience, 13(4),* 453-461.

Hou, J., Wu, W., Lin, Y., Wang, J., Zhou, D., Guo J., . . . , Li, H. (2012). Localization of cerebral functional deficits in patients with obsessive–compulsive disorder: a resting-state fMRI study. *Journal of Affective Disorders, 138,* 313-321.

Huff, W., Lenartz, D., Schormann, M., Lee, S., Kuhn, J., Koulousakis, A., . . . , Sturm, V. (2010). Unilateral deep brain stimulation of the nucleus accumbens in patients with treatment-resistant obsessive-compulsive disorder: Outcomes after one year. *Clinical Neurology and Neurosurgery. 112,* 137-143.

Israël, M., Steiger, H., Kolivakis, T., McGregor, L., & Sadikot, A. F. (2010). Deep brain stimulation in the subgenual cingulate cortex for an intractable eating disorder. *Biological Psychiatry. 67(9),* E53-4.

Jiménez, F., Nicolini, H., Lozano, A. M., Piedimonte, F., Salín, R., & Velasco, F. (2012). Electrical stimulation of the inferior thalamic peduncle in the treatment of major depression and obsessive compulsive disorders. *World Neurosurgery,* In Press.

Jiménez, F., Velasco, F., Salín-Pascual, R., Hernández, J. A., Velasco, M., Criales, J. L., & Nicolini, H. (2005). A patient with a resistant major depression disorder treated with deep brain stimulation in the inferior thalamic peduncle. *Neurosurgery, 57(3),* 585-593.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., Rush, A. J., Walters, E. E., & Wang, P. S. (2003). The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA, 289(23),* 3095-3105.

Kim, C-H., Jeong, J-W., Kim, E. J., Shin, Y. S., Suh, H. S., Lee, H., S., & Koo, M-S. (2011). Clinical predictors of drug response in patients with obsessive-compulsive disorder. *Clinical Psychopharmacology and Neuroscience, 9(1)*, 23-28.

Koning, de, P. P., Figee, M., Munchhof, van den, P., Schuurman, P. R., & Denys, D. (2011). Current status of deep brain stimulation for obsessive-compulsive disorder: a clinical review of different targets. *Current Psychiatry Reports, 13,* 274-282.

Kosel, M., Sturm, V., Frick, C., Lenartz, D., Zeidler, G., Brodesser, D., & Schlaepfer, T. E. (2007). Mood improvement after deep brain stimulation of the internal globus pallidus for tardive dyskinesia in a patient suffering from major depression. *Journal of Psychiatric Research, 41*, 801-803.

Krack, P., Hariz, M.I., Baunez, C., Guridi, J., & Obeso, J. A. (2010). Deep brain stimulation: from neurology to psychiatry? *Trends in Neurosciences, 33(10),* 474-484.

Kringelbach, M. L., Green, A. L., Owen, S. L. F., Schweder, P. M., & Aziz, T. Z. (2010). Sing the mind electric – principles of deep brain stimulation. *European Journal of Neuroscience, 32,* 1070-1079.

Kuhn, J., Gründler, T. O., Lenartz, D., Sturm, V., Klosterkötter, J., & Wolfgang, H. (2010). Deep brain stimulation for psychiatric disorders. *Deutsches Arzteblatt International, 107(7),* 105-118.

Kwaasteniet, de, B., Ruhe, E., Caan, M., Rive, M., Olabarriaga, S., Groefsma, M., . . . Denys, D. (2013). Relation between structural and functional connectivity in major depressive disorder. *Biological Psychiatry,* In Press.

Lagemann, T., Rentzsch, J., Montag, C., Gallinat, J., Jockers-Scherübl, M., Winter, C., & Reischies, F. M. (2012). Early orbitofrontal hyperactivation in obsessive-compulsive disorder*. Psychiatry Research, 202(3),* 257-263

Le Jeune, F., Vérin, M., N’Diaye, K., Drapier, D., Leray, E., Montcel, du, S. T., . . . Millet, B. (2010). Decrease of prefrontal metabolism after subthalamic stimulation in obsessive-compulsive disorder: a positron emission tomography study. *Biological Psychiatry, 68,* 1016-1022.

Leckman, J. F., Bloch, M. H., Smith, M. E., Larabi, D., & Hampson, M. (2010). Neurobiological substrates of Tourette’s disorder. *Journal of Child and Adolescent Psychopharmacology, 20(4),* 237-247.

Lee, J. H., Durand, R., Gradinaru, V., Zhang, F., Goshen, I., Kim, D-S., Fenno, L. E., Ramakrishnan, C., & Deisseroth, K. (2010). Global and local fMRI signals driven by neurons defined optogenetically by type and wiring. *Nature, 465,* 788-792.

Limousin, P., Greene, J., Pollak, P., Rothwell, J., Benabid, A. L., & Frackowiak, R. (1997). Changes in cerebral activity pattern due to subthalamic nucleus or internal pallidum stimulation in Parkinson's disease. *Annals of Neurology, 42(3),* 283-291.

Limousin, P., Pollak, P., Benazzouz, A., Hoffman, D., Le Bas, J-F., Broussolle, E., Perret, J. E., & Benabid, A-L. (1995). Effect on parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *Lancet, 345,* 91-95.

Lipsman, N., Woodside, D. B., Giacobbe, P., Hamani, C., Carter, J. C., Norwood, S. J., Sutandar, K., Staab, R., Elias, G., Lyman, C. H., Smith, G. S., & Lozano, A. M. (2013). Subcallosal cingulate deep brain stimulation for treatment-refractory Anorexia Nervosa: a phase 1 pilot trial. *The Lancet, 381(9875),* 1361-1370.

Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature, 412(6843),* 150-157.

Lopez, K. C., Lalonde, F., Mattai, A., Wade, B., Clasen, L., Rapoport, J., & Giedd, J. N. (2013). Quantitative morphology of the corpus callosum in obsessive–compulsive disorder. *Psychiatry Research: Neuroimaging, 212,* 1-6.

Lozano, A. N., & Lipsman, N. (2013). Probing and regulating dysfunctional circuits using deep brain stimulation (2013). *Neuron, 77,* 406-424.

Lozano, A. M., Mayberg, H. S., Giacobbe, P., Hamani, C., Craddock, R. C., & Kennedy, S. H. (2008). Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. *Biological Psychiatry, 64,* 461-467.

Lyons, M. K. (2011). Deep brain stimulation: current and future clinical applications. *Mayo Clinic Proceedings, 86(7),* 662-672.

Mallet, L., Mesnage, V., Houeto, J-L., Pelissolo, A., Yelnik, J., Behar, C., . . . Agid, Y. (2002). Compulsions, Parkinson’s disease, and stimulation. *Lancet, 360,* 1302-1304.

Mallet, L., Polosan, M., Jaafari, N., Baup, N., Welter, M-L., Fontaine, D., . . . Pelissolo, A. (2008). Subthalamic nucleus stimulation in severe obsessive-compulsive disorder. *The New England Journal of Medicine, 359(20),* 2121-2134.

Malone, D. A., Dougherty, D. D., Rezai, A. R., Carpenter, L. L., Friehs, G. M., Eskandar, E. N., . . . Greenberg, B. D. (2009). Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. *Biological Psychiatry, 65,* 267-275.

Malone, D. A. (2010). Use of deep brain stimulation in treatment-resistant depression. *Cleveland Clinic Journal of Medicine, 77(3),* S77-S80.

Martinez-Ferdandez, R., Zrinzo, L., Aviles-Olmos, I., Hariz, M., Martinez-Torres, I., Joyce, E., . . . Foltynie, T. (2011). Deep brain stimulation for Gilles de la Tourette syndrome: a case series targeting subregions of the globus pallidus internus. *Movement Disorders, 26(10),* 1922-1930.

Mayberg, H. S., Lozano, A. M., Voon, V., McNeely, H. E., Seminowicz, D., Hamani, C., Schwalb, J. M., & Kennedy, S. H. (2005). Deep brain stimulation for treatment-resistant depression. *Neuron, 45,* 651-660.

Mazars, G. J. (1975). Intermittent stimulation of nucleus ventralis posterolateralis for intractable pain. *Surgical Neurology, 4,* 93-95.

McIntyre, C. C., & Hahn, P. J. (2010). Network perspectives on the mechanisms of deep brain stimulation. *Neurobiology of Disease, 38,* 329-337.

McIntyre, C. C., Savasta, M., Kerkerian-Le Goff, L., & Vitek, J. L. (2004). Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. *Clinical Neurophysiology, 115,* 1239-1248.

Menzies, L., Chamberlain, S. R., Laird, A. R., Thelen, S. M., Sahakian, B. J., & Bullmore, E. T. (2008). Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. *Neuroscience and Biobehavioral Reviews, 32(3),* 525-549.

Mian, M. K., Campos, M., Sheth, S. A., & Eskandar, E. N. (2010). Deep brain stimulation for obsessive-compulsive disorder: past, present, and future. *Neurosurgery Focus, 29(2),* E10.

Milad, M. R., & Rach, S. L. (2010). Obsessive-compulsive disorder beyond segregated cortico-striatal pathways. *Trends in Cognitive Sciences, 16,* 1.

Mitchel, I. J., Clarke, C. E., Boyce, S., Robertson, R. G., Peggs, D., Sambrook, M. A., & Crossman, A. R. (1989). Neural mechanisms underlying parkinsonian symptoms based upon regional uptake of 2-deoxyglucose in monkeys exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Neuroscience, 32(1),* 213-226.

Moniz, E. (1937). Prefrontal leucotomy in the treatment of mental disorders. *American Journal of Psychiatry, 93,* 1379-1385.

Nabeyama, M., Nakagawa, A., Yoshiura, T., Nakao, T., Nakatani, E., Togao, O., . . . Kanba, S. (2008). Functional MRI study of brain activation alterations in patients with obsessive-compulsive disorder after symptom improvement. *Psychiatry Research: Neuroimaging. 163,* 236-247.

Neimat, J. S., Hamani, C., Giacobbe, P., Merskey, H., Kennedy, S. H., Mayberg, H. S., & Lozano, A. M. (2008). Neural stimulation successfully treats depression in patients with prior ablative cingulotomy. *American Journal of Psychiatry, 165(6),* 687-693.

Nuttin, B., Cosyns, P., Demeulemeester, H., Gybels, J., & Meyerson, B. (1999). Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder. *Lancet, 354,* 1999.

Nuttin, B. J., Gabriëls, L. A., Cosyns, P. R., Meyerson, B. A., Andréewitch, S., Sunaert, S. G., . . . Demeulemeester, H. G. (2003). Long-term electrical capsular stimulation in patients with obsessive-compulsive disorder. *Neurosurgery, 52(6),* 1263-1274.

Olds, J., & Milner, P. (1954). Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *Journal of Comparative and Physiological Psychology, 47,* 419-427.

Pandya, M., Altinay, M., Malone, D. A., & Anand, A. (2012). Where in the brain is depression? *Current Psychiatry Reports, 14,* 634-642.

Peng, Z., Lui, S. S. Y., Cheung, E. F. C., Jin, Z., Miao, G., Jing, J., & Chan, R. C. K. (2012). Brain structural abnormalities in obsessive-compulsive disorder: converging evidence from white matter and grey matter. *Asian Journal of Psychiatry, 5,* 290-296.

Piacentino, M., Pilleri, M., & Bartolomei, L. (2011). Hardware-related infections after deep brain stimulation surgery: review of incidence, severity and management in 212 single-center procedures in the first year after implantation. *Acta Neurochirurgica, 153,* 2337-2341.

Piedad, J. C. P., Rickards, H. E., & Cavanna, A. E. (2012). What patients with Gilles de la Tourette syndrome should be treated with deep brain stimulation and what is the best target? *Neurosurgery, 71(1),* 173-192.

Pietrini, F., Castellini, G., Ricca, V., Polito, C., Pupi, A., & Faravelli, C. (2011). Functional neuroimaging in Anorexia Nervosa: a clinical approach. *European Psychiatry, 26,* 176-182.

Pizzagalli, D. A., Holmes, A. J., Dillon, D. G., Goetz, E. L., Birk, J. L., Bogdan, R, . . . Fava, M. (2009). Reduced caudate and nucleus accumbens response to rewards in unmedicated individuals with major depressive disorder. *American Journal of Psychiatry, 166*, 702-710.

Pralong, E., Debatisse, D., Maeder, M., Vingerhoets, F., Ghika, J., & Villemure, J. G. (2003). Effect of deep brain stimulation of GPI on neuronal activity of the thalamic nucleus ventralis oralis in a dystonic patient. *Neurophysiology Clinique, 33*, 169-173.

Price, J. L., & Drevets, W. C. (2010). Neurocircuitry of mood disorders. *Neuropsychopharmacology, 35,* 192-216.

Price, J. L., & Drevets, W. C. (2012). Neural circuits underlying the pathophysiology of mood disorders. *Trends in Cognitive Science, 16(1),* 61-71.

Puigdemont, D., Pérez-Egea, R., Portella, M. J., Molet, J., Diego-Adeliño, de, J., Gironell, A., . . . Pérez, V. (2012). Deep brain stimulation of the subcallosal cingulate gyrus further evidence in treatment-resistant major depression. *International Journal of Neuropsychopharmacology, 5,* 121-133.

Radua, J., van den Heuvel, O. A, Surguladze, S., & Mataix-Cols, D. (2010). Meta-analytical comparison of voxel-based morphometry studies in obsessive-compulsive disorder vs other anxiety disorders. *Archives of General Psychiatry, 67(7),* 701-711.

Radua, J., & Mataix-Cols, D. (2009). Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. *British Journal of Psychiatry, 195(5),* 393-402.

Ranck, J. B. (1975). Which elements are excited in electrical stimulation of mammalian central nervous system: a review. *Brain Research, 98,* 417-440.

Raichle, M. E. (2001). Cognitive neuroscience: bold insights. *Nature, 412,* 128-130.

Rauch, S. L., Dougherty, D. D., Malone, D., Rezai, A., Friehs, G., Fischman, A. J., . . . Greenberg, M. D. (2006). A functional neuroimaging investigation of deep brain stimulation in patients with obsessive-compulsive disorder. *Journal of Neurosurgery, 104(4),* 558-565.

Robertson, M. M. (2012). The Gilles de la Tourette syndrome: the current status. *Archives of Disease in Childhood, 97,* 166-175.

Ruscio, A. M., Stein, D. J., Chiu, W. T., & Kessler, R. C. (2010). The epidemiology of obsessive compulsive disorder in the National Comorbidity Survey Replication. *Moleculair Psychiatry, 15(1),* 53-63.

Saleh, C., Gonzalez, V., Cif, L., & Coubes, P. (2012) Deep brain stimulation of the globus pallidus internus and Gilles de la Tourette syndrome: toward multiple networks modulation. *Surgical Neurology International: Stereotactic, 3(2),* S127-142.

Sartorius, A., Kiening, K. L., Kirsch, P., Gall, von, C. C., Haberkorn, U., Unterberg, A. W., Henn, F. A., & Meyer-Lindenberg, A. (2010). Remission of major depression under deep brain stimulation of the lateral habenula in a therapy-refractory patient. *Biological Psychiatry, 67,* e9–e11.

Schlaepfer, T. E., Bewernick, B., Kayser, S., & Lenz, D. (2011). Modulating affect, cognition, and behavior - prospects of deep brain stimulation for treatment-resistant psychiatric disorders. *Frontiers in Integrative Neuroscience, 5(29),* 1-6.

Schlaepfer, T. E., Bewernick, B. H., Kayser, S., Mädler, B., & Coenen, V. A. (2013). Rapid effects of deep brain stimulation for treatment-resistant major depression: DBS at supero-lateral branch of the medial forebrain bundle in seven patients with highly refractory depression. *Biological Psychiatry,* In Press.

Schlaepfer, T. E., Cohen, M. X., Frick, C., Kosel, M., Brodesser, D., Axmacher, N., . . . Sturm, V. (2008). Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacology, 33,* 368-377.

Schneider, T. M., Beynon, C., Sartorius, A., Unterberg, A. W., & Kiening, K. L. (2012). Deep brain stimulation of the lateral habenular complex in treatment-resistant depression: traps and pitfalls of trajectory choice. *Neurosurgery,* In Press.

Servello, D., Sassi, M., Brambilla, A., Defendi, S., & Porta, M. (2009). Long-term, post-deep brain stimulation management of a series of 36 patients affected with refractory Gilles de la Tourette syndrome. Neuromodulation: *Technology at the Neural Interface, 10(13),* 187-194.

Shields, D. C., Cheng, M. L., Flaherty, A. W., Gale, J. T., & Eskandar, E. N. (2008). Microelectrode-guided deep brain stimulation for Tourette Syndrome: within-subject comparison of different stimulation sites. *Stereotactic and Functional Neurosurgery, 86,* 87-91.

Skoog, G., & Skoog, I. (1999). A 40-year follow-up of patients with obsessive-compulsive disorder. *Archives of General Psychiatry, 56,* 121-127.

Spiegel, E. A. (1950). Pallidothalamotomy in chorea. *Archives of Neurology and Psychiatry, 64(2),* 295-296.

Spiegel, E. A., Wycis, H. T., Marks, M., & Lee, A. J. (1947). Stereotaxic apparatus for operations on the human brain. *Science, 106*, 349-350.

Sun, B., & Liu, W. (2013). Stereotactic surgery for eating disorders. *Surgical Neurology International, 4(3),* S164-S169.

Taghva, A. S., Malone, D. A., & Rezai, A. R. (2012). Deep brain stimulation for treatment-resistant depression. *World Neurosurgery,* In Press.

Titova, O. E., Hjorth, O. C., Schiöth, H. B., & Brooks, S. J. (2013). Anorexia Nervosa is linked to reduced brain structure in reward and somatosensory regions: a meta-analysis of VBM studies. *BMC Psychiatry, 13(110),* 1-11.

Urbano, F. J., Leznik, E., & Llinás, R. R. (2002). Cortical activation patterns evoked by afferent axons stimuli at different frequencies an in vitro voltage-sensitive dye imaging study. *Thalamus & Related Systems, 1(4),* 371-378.

Van Laere, K., Nuttin, B., Gabriels, L., Dupont, P., Rasmussen, S., Greenberg, B. D., & Cosyns, P. (2006). Metabolic imaging of anterior capsular stimulation in refractory obsessive-compulsive disorder: a key role for the subgenual anterior cingulate and ventral striatum. *Journal of Nuclear Medicine, 47(5),* 740-747.

Vandewalle, V., Linden, van der, C., Groenewegen, H. J., & Caemaert, J. (1999). Stereotactic treatment of Gilles de la Tourette syndrome by high frequency stimulation of thalamus. *Lancet, 353(9154),* 724.

Vernaleken, I., Kuhn, J., Lenartz, D., Raptis, M., Huff, W., Janouschek, H., . . . Sturm, V. (2009). Bithalamical deep brain stimulation in Tourette syndrome is associated with reduction in dopaminergic transmission. *Biological Psychiatry. 66(10),* E15-E17.

Volkmann, J., Moro, E., & Pahwa, R. (2006). Basic algorithms fort the programming of deep brain stimulation in Parkinson’s disease. *Movement Disorders, 21,* S284-S289.

Wang, Z., Maia, T. V., Marsh, R., Colibazzi, T., Gerber, A., & Peterson, B. S. (2011). The neural circuits that generate tics in Tourette’s syndrome. *American Journal of Psychiatry, 168*, 1326-1337.

Whiteside, S. P., Port, J. D., & Abramowitz, J. S. (2004). A meta-analysis of functional neuroimaging in obsessive-compulsive disorder. *Psychiatry Research: Neuroimaging, 132,* 69-79.

Wu, H., Van Dyck-Lippens, P. J., Santegoeds, R., Kuyk, van, K., Gabriëls, L., Lin, G., . . . Nuttin, B. (2013). Deep-Brain stimulation for Anorexia Nervosa. *World Neurosurgery,* In Press.

Zqbek, M., Sobstyl, M., Koziara, H., & Dzierzecki, S. (2008). Deep brain stimulation of the right nucleus accumbens in a patient. *Neurologia i Neurochirurgia Polska, 42*, 554-559.